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FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,195	PEPICELLI ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 19-26* is/are pending in the application.

4a) Of the above claim(s) *5-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 19-26* is/are rejected.

7)☒ Claim(s) 21 is/are objected to.

8)☒ Claim(s) *1-17 and 19-26* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 May 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/5/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/6/07 has been entered.

Status of Application, Amendments and/or Claims

The amendment of 2/6/07 has been entered in full. Claims 1-4 and 19-26 are amended. Claim 18 was cancelled previously. Claims 5-17 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1-4 and 19-26 are under consideration in the instant application.

Information Disclosure Statement

The Information Disclosure Statement of 4/5/07 has been considered.

Withdrawn Objections and/or Rejections

The following page numbers refer to the 8/3/06 Office Action.

The objection to claims 1, 2 and 19-22 at pg 4 is *withdrawn* in view of Applicants' amendments to these claims to italicize the term "*ptc*".

The rejection of claims 1, 3, 4, 25 and 26 at pg 5-11 for lack of enablement is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claims 2 and 19-24 at pg 5-11 for lack of enablement is *withdrawn in part* in view of Applicants' amendments to the claims. Specifically, the rejection is *withdrawn* it related to methods of treatment. However, the rejection is maintained in relation to the amended claims directed to methods of screening.

The rejection of claim 23 under 35 U.S.C § 112, second paragraph, at pg 12 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants' amendments to the claims.

Claim Objections

Claim 21 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 21 depends from claim 1 and limits the method to one wherein "*ptc* therapeutic is a small organic molecule". However, claim 1 recites "wherein the agent is a *ptc* therapeutic and wherein the agent is a small organic molecule". Therefore, claim 21 fails to further limit the agent used in the method of claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 19-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(1) a method of screening for an agent for inducing the formation of, or the maintenance or functional performance of normal lung tissue, comprising contacting embryonic lung tissue from a *Shh* mutant mouse with an agent and determining, as compared to a control, whether the agent promotes hedgehog/patched signal transduction and whether the agent induces the formation of, or the maintenance or functional performance of normal lung tissue,

does not reasonably provide enablement for

(2) a method of screening for an agent for inducing the formation of, or the maintenance or functional performance of normal lung tissue, comprising contacting

lung tissue with an amount of an agent and determining, as compared to a control, whether the agent promotes hedgehog/patched signal transduction and whether the agent induces the formation of, or the maintenance or functional performance of normal lung tissue.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention of claims 2 and 19-24 is a method of screening comprising contacting lung tissue with an agent is a *ptc* therapeutic and determining if the agent promotes patched signal transduction and induces formation and induces the formation of, or the maintenance or functional performance of normal lung tissue. Claim 2 encompasses any type of *ptc* therapeutic whereas claims 19-24 limit the nature of the ptc therapeutic to particular embodiments.

The specification provides the following working examples in support of claims 2 and 19-24. The specification teaches that at 12.5 days *post coitum* (dpc) of embryonic mouse development, *Sonic hedgehog* (*Shh)* mutant mice have lung buds that "have not branched or possess one abnormally positioned branch point (Figure 1f)". At later days (15.5 and 18.5 dpc), "*Shh* mutants form only a rudimentary respiratory organ with a few large, poorly vascularized airways (Figure 1h)". The specification further teaches that expression of the genes patched (Ptc-1) and Gli-1 is only observed at basal levels in the Shh mutants. The specification further teaches, "[w]ild-type lungs undergo considerable growth and branching in organ culture. However, in explant culture of lungs from *Shh* mutants, bronchial mesenchyme cells detach from the endoderm and the epithelium fails to grow, or branch extensively (data not shown)".

In addition to the working examples, the specification teaches that the subject methods of the invention can be "performed on cells which are provided in culture (in

vitro), or on cells in a whole animal (in vivo)" (pg 10, lines 21-22). The specification further teaches (starting at pg 48) methods of screening to identify a *ptc* therapeutic, including an assay that "scores for the ability of a test compound to alter the signal transduction activity of the *patched* protein". The specification teaches that such assays can be used to identify proliferative and anti-proliferative ptc therapeutics (pg 48, lines 18-19).

In view of the teachings of the specification, the skilled artisan could perform a method of screening comprising contacting embryonic lung tissue from a *Shh* mutant mouse with a test agent and determining whether hedgehog/patched signal transduction was promoted (by assessing Ptc-1 or Gli-1 gene expression) and whether "normal" or functional lung tissue was formed. Such a method could be performed either *in vivo* using the Shh mutant mice, or *in vitro* using lung explant culture. However, the claims are not limited to such methods. Instead, the claims broadly encompass a method of screening using "lung tissue" rather than being limited embryonic lung tissue from a *Shh* mutant.

The genus of "lung tissue" used in the claims encompasses lung tissue from a variety of sources, including embryonic lung tissue from *Shh* mutant or wildtype organisms, adult normal or injured lung tissue, and lung cancer tissue. Formation of "normal lung tissue" encompasses both *in vitro* formation of lung tissue (e.g., lung cell culture or lung "explant" organ culture) and *in vivo* formation of tissue (e.g., production of adult lung tissue from either fetal lung tissue or damaged adult lung tissue). The term "normal lung tissue" excludes "abnormal lung tissue" and implies that the newly formed tissue must be functional. Furthermore, the claims require that the agent induces formation, maintenance or functional performance of said "normal lung tissue".

It is clear from the teachings of the specification and prior art that Shh plays an important role in the development of the lung. However, the relevant art also makes it clear that lung morphogenesis is extremely complex, and that Shh is only one of a large number of factors involved in this process. For example, Warburton (2000) teaches, "Lung morphogenesis is determined by functional integration of key transcriptional factors, peptide growth factor receptor-mediated signaling, extracellular matrix, integrin

and non-integrin signaling. These inputs are integrated during the normal process of embryonic, fetal and postnatal lung morphogenesis. They instruct organized temporo-spatial patterns of cellular proliferation, cell lineage differentiation, cell movement and cell death that determine structure and hence physiological function" (pg 57 of Warburton et al 2000; cited previously)." Kumar (2004) teaches, "Formation and orderly development of the mammalian lung results from a complex set of cell to cell and cell to matrix interactions following transcriptional regulation during pulmonary organogenesis. Transcriptional control of differentiation genes early on and epithelial-mesenchymal interactions mediated by growth factors later on, resulting in the formation of conducting airways and an extensive alveolar capillary interface, is critical for normal lung development" and "[e]pithelial-endothelial interactions during lung development are important in establishing a functional blood gas interface. Epithelial-mesenchymal interactions mediated by growth factors are also important in the restoration of normal alveolar architecture after lung injury. Further understanding of the role of these growth factors and their cellular interactions in bronchopulmonary dysplasia and in tissue repair following lung injury, may lead to development of better therapeutic modalities in treating these disorders" (pg 464 of Kumar et al. 2004. Frontiers in Bioscience. 9: 464-480; cited previously). Kumar (2004) also teaches that the *in vivo* processes of lung development and repair remained poorly understood, even as of 2004:

> "Even though it is important to study the effects of individual growth factors on isolated cell preparations, there are multiple growth factors present in vivo at different times during lung development and during the lung injury and repair process. The complex interactions among growth factors and the spatial and temporal relationship to cellular proliferation and differentiation might be different in vivo and is as yet unclear. The effects of a particular growth factor may be different at different sites and at different time points. The dynamic interplay among type II cells, the extracellular matrix and various growth factors may determine multicellular functions and play an important role in normal lung development and in repair of the lung epithelium following injury. A better understanding of the epithelial-endothelial interaction and regulation of the alveolar-capillary interface will provide important clues for novel therapies in preterm infants with chronic lung injury" (pg 474).

In view of the limited teachings of the specification, and the teachings of the relevant art regarding the complexity of lung tissue formation, it is unpredictable whether or not lung tissue other than embryonic lung tissue from a *Shh* mutant can be used in the claimed method of screening. Due to the complexity of production of "normal lung

tissue" (as taught in the references cited above), the skilled artisan at the time of filing of the instant application could not predict whether or not a compound that promotes patched signal transduction could also induce formation of normal lung tissue. Even if a compound were found to promote patched signaling, it may or may not produce normal lung tissue. Embryonic lung tissue from a *Shh* mutant is missing a single component required for production of normal lung tissue and the skilled artisan would predict that other single compounds could be isolated in a screening method that would function in place of *Shh*. However, it is not predictable whether or not a single "agent" could be added to other types of lung tissue and result in the formation of "normal lung tissue". For example, it is not predictable whether or not a single agent can be added to normal adult lung tissue in a manner that results in formation of normal adult lung tissue. Furthermore, the prior art at the time of filing would lead the skilled artisan to conclude that addition of an agent that promotes *ptc* signaling may result in abnormal rather than normal lung tissue production.

For example, the prior art teaches that overexpression of *Shh* during development produces mice with abnormal lung tissue at birth (see pg 56 of Bellusci et al. 1997; cited on the 12/3/03 IDS). Therefore, the skilled artisan at the time of filing of the instant application would predict that if embryonic lung tissue from a normal mouse (expressing *Shh*) were contacted with a *ptc* therapeutic, it would result in abnormal rather than normal lung tissue formation. Therefore, it is unpredictable whether or not the claimed method of screening can be used with lung tissues from animals that are not *Shh* deficient. The instant specification provides no teachings regarding the level of Shh expression in normal or injured adult lung tissue. The skilled artisan could not predict whether or not promotion of patched signaling in adult tissue would result in formation of normal tissue, abnormal tissue, or have no effect. It would require undue experimentation to determine whether or not the Shh protein itself, let alone other patched promoting agents, could be used to form functional lung tissue. Such experimentation would be required before a method of screening could be used.

Furthermore, the term lung tissue is not defined in the specification and encompasses a variety of lung cancer tissues, including an *in vivo* tumor, explanted

tumor tissue, and cultured lung cancer cell lines. Therefore, the claims broadly encompass formation of normal lung tissue from lung cancer cells. However, the prior art teaches that the N-terminal fragment of Sonic hedgehog (Shh-N) is capable of stimulating *in vitro* proliferation of lung squamous carcinoma cells, and that anti-Shh-N antibody inhibits proliferation (see pg 661 of Fujita et al 1997, cited in the 9/20/05 Office Action). In view of the teachings of Fujita with Sonic hedgehog, the skilled artisan would predict that a compound that activates patched signaling would promote lung cancer growth rather than formation of normal lung tissue. Therefore, the claims also lack enablement for this encompassed embodiment.

With respect to methods of screening using *Shh* mutant animals of species other than mouse, there are no methods or working examples disclosed in the instant application indicating that a multicellular animal other than a mouse has the claimed gene "knocked out". The unpredictability of the art is *very high* with regards to making transgenic animals, particularly at the date of priority claimed by the instant application (1998). For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). The literature teaches that the production of transgenic animals by microinjection of embryos suffers from a number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome that may disrupt or interfere with critical endogenous gene expression (Wigley et al. Reprod Fert Dev 6: 585-588, 1994). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even more rare than random events. Therefore, in view of the extremely low frequency of both targeted and non-targeted homologous recombination events in microinjected

embryos, it would have required undue experimentation for the skilled artisan to have made any and all transgenic non-human animals according to the instant invention. Furthermore, regarding gene targeting in embryonic stem cells, the specification does not provide guidance for identifying and isolating embryonic stem cells or for identifying other embryonal cells that are capable of contributing to the germline of any animal. At the time of filing, Campbell et al. teaches that, "in species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines in a number of species...However, as yet there are not reports of any cell lines which contribute to the germ line in any species other than mouse" (Campbell et al. Theriology 47(1): 63-72, 1997; see pg 65, 2nd paragraph). Thus, based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than mice to produce transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells that can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology.

In summary, it is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification whether lung tissue other than embryonic lung tissue from *Shh* mutant mice can be used in a method of screening for agents that promote patched signaling and induce formation of, or the maintenance or functional performance of normal lung tissue. The specification fails to teach the skilled artisan how to use the claimed methods without resorting to undue experimentation. The specification merely invites the skilled artisan to engage in further undue experimentation to determine whether or not an agent that promotes patched signaling can also induce formation of, maintenance or functional performance of normal lung tissue from the range of lung tissue sources encompassed by the claims.

Applicants' arguments (2/6/07; pg 8-9) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the previous basis for rejection is no longer applicable to the amended claims. Applicants submit that the independent claims have been amended to be directed to methods of screening for agents. Applicants argue that a skilled artisan need not identify molecules having the recited activity prior to performing the claimed method and that the specification adequately enables a skilled artisan to perform the claimed methods of screening.

Applicants' arguments have been fully considered but are not found persuasive. It is noted that the claims have been amended. The enablement rejection has been withdrawn for the claimed method of screening to identify inhibitors of lung cancer proliferation. However, for the reasons set forth above, the claimed methods lack enablement for methods of screening for compounds that induce formation of, or the maintenance or functional performance of normal lung tissue.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1-4, 19-21, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 and dependent claims 3, 4, 21, 25 and 26 encompass "a method of screening for an agent inhibiting or reducing proliferation or growth of lung cancer cells, comprising contacting lung cancer cells with an amount of an agent, wherein the agent is a *ptc* therapeutic and wherein the agent is a small organic molecule..." As set forth in the section titled, "Claim Rejections - 35 U.S.C. 112, 2nd Paragraph", the claims have been interpreted broadly to encompass a method of screening using a known *ptc* therapeutic that is small organic molecule. The specification teaches that the term ""ptc therapeutic" refers to agents which either (i) mimic the effect of hedgehog proteins on patched signalling, e.g., which antagonize the cell-cycle inhibitory activity of patched, or

(ii) activate or potentiate patched signalling." However, the specification fails to describe any small organic molecules that are "*ptc* therapeutics" other than inhibitors of protein kinase A.

Claims 2 encompasses "a method of screening for an agent for inducing the formation of, or the maintenance or functional performance of normal lung tissue, comprising contacting lung tissue with an amount of an agent wherein the agent is a *ptc* therapeutic..." However, the specification fails to describe a genus of ptc therapeutics to be used in the claim. The specification envisions a genus of "ptc therapeutics" including peptides, nucleic acids, carbohydrates, small organic molecules, and natural product extracts. However, the only specific ptc therapeutics that appear to be describe by the specification are the hedgehog proteins, inhibitors of protein kinase A, and antisense constructs that inhibit fused, costal-2, smoothened and Gli gene expression.

Claim 19 depends from claim 2 and limits the ptc therapeutic to a "small organic molecule which binds to a patched protein". However, the specification fails to describe any small organic molecules that bind to patched protein.

Claim 20 depends from this claim and limits the *ptc* therapeutic to one that binds to patched and mimics hedgehog. However, the only specific *ptc* therapeutic that binds to patched that appear to be describe by the specification are the hedgehog proteins.

Claim 21 depends from claim 2 and limits the "*ptc* therapeutic" to a small organic molecule. However, the specification fails to describe any small organic molecules that are "*ptc* therapeutics" other than inhibitors of protein kinase A.

As set forth previously, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

Applicants' arguments (2/6/07; pg 9) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the previous basis for rejection is no longer applicable to the amended claims. Applicants submit that the independent claims have been amended to be directed to methods of screening for agents. Applicants

submit that the specification adequately discloses methods for screening for molecules (including small organic molecules) having the recited activities.

Applicants' arguments have been fully considered but are not found persuasive. It is noted that the claims have been amended. However, the claims as amended recite methods of using a genus of "*ptc* therapeutics" that are not described in the specification.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 19-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it recites, "wherein the agent is a ptc therapeutic" and "determining, as compared to a control, whether the agent inhibits or attenuates hedgehog/patched signal transduction" and "if the agent inhibits or attenuates the hedgehog/patched signal transduction". It is unclear whether the claimed method is limited to a method of screening with a known "a *ptc* therapeutic" (i.e., a compound that was previously identified as a *ptc* therapeutic prior to performing the method of screening), or whether the claim encompasses a method of screening with an agent that is identified as "a *ptc* therapeutic" by the method (i.e., a compound that inhibits or attenuates hedgehog/patched signal transduction as determined by the method). For purposes of prosecution, the claim has been interpreted broadly to encompass either possibility.

Claim 1 is also indefinite because it recites "hedgehog/patched signal transduction". This term is not defined in the specification or used in relation to any of the screening assays used in the specification.

Independent claim 2 is indefinite for both the same reasons as claim 1 above.

Claim 3 recites the limitation "the lung cancer cell" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 4 depends from claim 1, which recites "lung cancer cells" (plural). Therefore, the recitation of "the lung cancer cell" (singular) in claim 3 is indefinite.

Claim 4 recites the limitation "the cell" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 4 depends from claim 1, which recites "lung cancer cells" (plural). Therefore, the recitation of "the cell" (singular) in claim 3 is indefinite.

Claim 4 is also indefinite because it depends from claim 1, which is directed to a method of screening but recites, "wherein the cell is treated in an animal and the agent is administered to the animal as a therapeutic composition". In the parent claim, the cell is contacted with the agent; it is unclear what constitutes treatment and/or a therapeutic composition in claim 4. For purposes of prosecution, claim 4 has been interpreted broadly to encompass any method of claim 1 wherein the cell is contacted in an animal (*in vivo*) and administered in a composition.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 4, 21, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marigo et al (U.S. Patent No. 6,261,786, published 7/17/01, filed 7/2/96 and claiming priority to 12/30/93) in view of Fujita et al (9/18/1997, Biochemical and Biophysical Research Communications, 238: 658-665; cited previously).

The recitation of "screening for an agent for inhibiting or reducing the proliferation or growth of lung cancer cells" in the preamble of the claim 2 from the instant application

is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. Furthermore, as set forth in the section titled, "Claim Rejections - 35 U.S.C. 112, 2nd Paragraph", the claim has been interpreted broadly to encompass a method using an agent that is identified as a *ptc* therapeutic by performing the claimed method (i.e., an agent that is identified as a *ptc* therapeutic by inhibiting hedgehog/patched signal transduction as determined by the method). Therefore, claim 1 encompasses a method comprising contacting lung cancer cells with an agent that is a small organic molecule, and determining, as compared to a control, whether the agent inhibits (1) hedgehog/patched signal transduction and (2) cell proliferation.

Marigo teaches "cell-based assays for identifying small molecule agonists/antagonists" (col 51, lines 24-25). Marigo teaches that "cells which are sensitive to hedgehog induction, e.g. patched-expressing cells, can be contacted with a hedgehog protein and a test agent of interest, with the assay scoring for anything from simple binding to the cell to modulation in hedgehog inductive responses by the target cell in the presence and absence of the test agent. As with the cell-free assays, agents which produce a statistically significant change in hedgehog activities (either inhibition or potentiation) can be identified" (col 51, lines 27-35). Marigo further teaches that patched gene expression is responsive to Shh signaling. Marigo further teaches that the test compounds to be used in the screening methods include "small organic molecules" (see claim 27). Marigo further teaches that "[a]fter identifying certain test compounds as potential modulators of the target hedgehog receptor activity, the practitioner of the subject assay will continue to test the efficacy and specificity of the selected compound both in vitro and in vivo ... for subsequent in vivo testing ... agents identified in the subject assay can be formulated in pharmaceutical preparations for in vivo administration to an animal, preferably a human".

Marigo does not teach a method of screening using lung cancer cells.

Fujita teaches "Shh-N stimulated the cell growth of LK-2 cells, while anti-Shh-N inhibited the cell growth of LK-2 cells (Figure 5). Thus Shh of LK-2 cells seem to stimulate their own cell growth through interaction with PTC by an autocrine

mechanism. LK-2 cells are useful for the study on the Shh-PTC signal involved in the cell proliferation". The growth assays were performed in cell culture and the Shh-N or anti-Shh-N was added to the culture medium (see Materials and Methods on pg 659-660). LK-2 is a human lung squamous carcinoma cell line (see Abstract). Fujita further describes detection of patched gene expression in the LK-2 cells (pg 660). Fujita further teaches that "Shh was also positive in the three lung squamous carcinoma tissues...while Shh was negative the epithelium of normal lung tissue of the same patients" (pg 661).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to perform a method of screening comprising contacting a cell culture of the LK-2 lung cancer cells taught by Fujita with a small organic molecule as taught by Marigo and measure hedgehog signaling pathway (by measuring patched gene expression) as taught by Marigo and growth as taught by Fujita. The person of ordinary skill in the art would have been motivated to do so to identify a small organic molecule that is an antagonist (inhibitor) of hedgehog signaling and lung cancer cell growth.

The method that is obvious over Marigo in view of Fujita meets the limitations of claims 1, 3, 21, 25 and 26. It is noted that the LK-2 lung squamous cell carcinoma cells meet the additional limitations presented in claims 25 and 26 because squamous cell carcinoma is a form of non-small cell lung cancer (claim 25) and is both a lung cell carcinoma and a squamous cell carcinoma (claim 26).

It would have further been obvious to the person of ordinary skill in the art at the time the invention was made to further modify the method of Marigo in view of Fujita described above to perform an in vivo method of screening comprising contacting the lung squamous carcinoma cells in a patient taught by Fujita with a small organic molecule that is administered as a composition as taught by Marigo. The person of ordinary skill in the art would have been motivated to do so in order to identify a small organic molecule that is an antagonist (inhibitor) of hedgehog signaling and lung squamous cancer cell growth in a patient.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Elizabeth C. Kemmerer

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ELIZABETH KEMMERER
PRIMARY EXAMINER